

REMARKS

Applicant has carefully considered the grounds for rejection of Claims 1-25 under 35 U.S.C. subsection 103(a) as being unpatentable over Nagy et al. (5,047,230) in view of Purewal et al (5,766,573).

Applicant respectfully traverses the rejection on the grounds that neither of the references either per se or taken in combination, are citable against the present application since, contrary to the view of the Examiner, they not only do not suggest the present invention, but in fact can be considered to teach away from it.

The primary reference, namely, Nagy et al., is directed to an aerosol composition free of propellant gas comprising, as active ingredient, nitroglycerin and ethyl alcohol. This reference, therefore, has no relevance whatsoever with respect to Claim 1A(i) which requires the use of a propellant Claim 1 Section (B) and Section (B(i) which require the use of a non-polar solvent. It is furthermore not relevant with respect to Claim I Section (A) which requires the use of an aqueous polar solvent no such solvent is disclosed in Nagy. However, applicant's position is not limited to the foregoing, but in fact, rests on a far greater difference.

Nitroglycerin is widely accepted in the pharmaceutical arts as being a very special case. It is almost unique in pharmaceutically active materials in that it is of low molecular weight and is readily transported across skin barriers even without a penetration enhancer. In the view of these special properties no person skilled in the art

would be led to the suggestion that because nitroglycerin can be administered by the methodology of Nagy et al that other pharmaceutically active materials would similarly be administrable. Indeed, based upon the data in this reference, it can be seen that the absorption phase is very short, with maximum concentrations being reached at five minutes and falling levels after five minutes. These results would reinforce the concept that the residence time in the mouth is short, and the time available for absorption is short, and hence, there is no suggestion that materials which are not absorbed as rapidly as nitroglycerin could be suitably administered by the methods of the present invention. This entire question is dealt with in greater detail by a monograph by applicant and coworkers a prepublication text of which is enclosed herewith for the Examiner's consideration and as an illustration of how the art, rather than the Examiner, views the problem in hand.

Furthermore, while the broad language of Nagy at Column 1, Line 14 does indeed mention buccal administration, the teaching of the reference as a whole does not support the position that the subject matter of Nagy suggests buccal administration. In fact, Column 2, Line 30 et. seq. coupled with the language Claim 1 makes it entirely clear that the intention of Nagy is to administer bioactive materials by inhalation into the lung which is an entirely different method of pharmaceutical administration than buccal absorption.

Applicant does not wish to reach the question as to whether the administration of suspensions of bioactive materials into the lung is desirable, they

would merely comment that the presence of particulate matter within the lung is known, in many cases, to have undesirable side effects.

Finally, it is pointed out that there is nothing in Nagy to suggest to one skilled in the art that a hydrocarbon could be considered as the sole propellant. All of the formulations in Nagy require the presence of a fluoro hydrocarbon as the main propellant with the hydrocarbon component itself constituting, in the illustrated examples, approximately 30 percent in most examples, and about 12 percent of the fluoro hydrocarbon propellant in other examples, in no case is the hydrocarbon itself shown or suggested as the sole propellant agent.

It is further applicant's position that the combination of Purewal with Nagy does nothing to enhance the Examiner's opinion that references are together suggest the present invention. The Examiner is correct that a substantial range of medicaments is disclosed at Column 3 Line 42 et seq. of Purewal. However, the Examiner's attention is drawn to the fact that the claims of the present application call for the active compound as being soluble in polar and non-polar solvents. The entire gist of Purewal as disclosed generally that Column 5 with particular attention to Line 43 and the paragraphs starting at Column 6, Line 28, and 30-37 coupled with all of the examples shown is directed at suspensions of solid materials rather than solutions, hence, there is no incentive to one skilled in the art to consider the disclosure of Purewal to be applicable to solutions.

Conclusion

In view of the foregoing comments, it is respectfully submitted that the references cited by the Examiner are untenable as bases of rejection under 35 U.S.C. 103(a) and therefore, this ground of rejection should be withdrawn and the application allowed and promptly passed to issue.

No fees are believed to be due in connection with the submission of this Response. If, however, any such fees, including extension fees, are due, the Examiner is authorized to charge them to Deposit Account No. 19-1218.

Respectfully Submitted,

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List of References:

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2. A. H. Shojaei. Buccal mucosa as a route for systemic drug delivery: a review.
J Pharm Pharm Sci. 1:15-30, 1998.
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quinones as endogenous tumor initiators. Pro. Natl. Acad. Sci. 94:10937-
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deren Herstellung. Patent DE 3922 650 A1, Issued Jan 11, 1990.
5. W. Cholcha. Nitroglycerin-Pumpspray. Patent DE 4007 705 C1. Issued Sept.
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Patent EU 0471 969 A1. Issued Feb. 12, 1991.
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Wirkstoffen. Patent DE 4038 203 A1. Issued June 4, 1992.
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la douleur accompagnant l'angine de poitrine. Patent FR-A-2735. Issued
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10. J. A. Deihl. Sprayable Analgesic Composition and Method of Use. Patent WO 94/13280. Issued June 23, 1994.
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13. R. Baker, G. Santus, and S. Vintilla-Friedman. Method and Therapeutic System for Smoking Cessation. Patent US 5,593,684. Issued Jan. 14, 1997.
14. A. Hegasy and K. Rämisch. Dihydropyridinspray, Verfahren zu seiner Herstellung and seine pharmazeutische Verwendung. Patent DE 3544 692 A1. Issued June 19, 1987.
15. K. Fömming, G. Neugebauer, N. Rietbrock and B. Woodcock. Verapamil and Gallopamil und ihre physiologisch verträglichen Salze zur resorptiven Anwendung auf Schleimhäuten des Mundes, des Nasen-Rachen-Räums und des Rektums. Patent DE 3338 978 A1. Issued May 3, 1984.
16. J. Fassberg, J. Sequeira and M. Kopcha. Non-Chlorofluorocarbon Aerosol Formulations. Patent US 5,474,759. Issued Dec. 12, 1995.
17. H. Dugger. Buccal Polar Spray or Capsule. Patent US 6,110,486. Issued August 29, 2000.
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Immediate-Immediate Release (I²R) Lingual or Buccal Spray Formulations for Transmucosal Delivery of Drug Substances

Title : Immediate-Immediate Release (I²R) Lingual or Buccal Spray Formulations for Transmucosal Delivery of Drug Substances

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I. Introduction:

Mucosal delivery of drugs has been reviewed^{1,2} extensively mainly from a sustained delivery point of view using buccal patches, muco-adhesives and other means for delivery to prolong the contact of the substance to be absorbed with the mucosal membrane. Immediate-Immediate Release (I²RTM) lingual or buccal spray technology, which is the subject of this paper, is quite different from these other methods in that these formulations do not require these means to prolong contact with the buccal mucosa. The term Immediate-Immediate Release is used because these formulations enable the drug to reach the systemic circulation faster than standard immediate release tablets, capsules and other oral formulations. The formulations employed for these purposes are usually designated either as "Lingual Sprays" or "Buccal Sprays" but in this chapter the term lingual sprays will be used throughout.

Oral lingual sprays are sprayed directly into the oral cavity onto the tongue and buccal tissue. The drug substance is transported in part through the oral mucosa directly into the bloodstream. Since less drug travels through the gastrointestinal tract, the loss due to the First Pass effect (metabolism by the liver during the absorption phase) is reduced. Because of the rapid delivery of drug into the systemic circulation, for the first time an oral route may accomplish the immediate treatment of symptoms using dosing-as-needed regimens (PRN dosing). In some cases the drug must be given in large quantities because the

first pass metabolism will remove most of the drug before it reaches systemic circulation. Lingual sprays, which avoid the first pass effect, allow one to use much smaller doses and achieve the same therapeutic effect. The lower dose is most important where metabolism leads to reactive intermediates that can bind to DNA and/or RNA. Cavalieri et al³ have proposed just such a metabolite to explain the carcinogenic potential of estradiol and estrone. Hence, I²R delivery puts an active therapeutic agent into the bloodstream, safely and rapidly, without the use of invasive techniques. Table 1 compares I²R formulations with some other technologies currently being used to attempt fast delivery at a lower dose.

Current Applications:

Nitroglycerin lingual spray (marketed as Nitrolingual® Spray in the USA) was the first commercially successful lingual spray product. Lingual sprays of other nitrate esters such as isosorbide dinitrate and mono-nitrate have also been reported but because of the larger dose required these lingual sprays were not as medically interesting as the nitroglycerin lingual spray. Patents⁴⁻⁸ in this area and published literature⁹ indicate that lingual absorption of nitroglycerin was very fast with a maximum plasma level concentration (C_{MAX}) being reached in 5-8 minutes with an equally fast decline in these levels over a period of 30 minutes. Two possible explanations for this rapid raise and equally rapid decline in plasma levels are:

1. The time for penetration of the mucosal membrane was very short before the nitroglycerin was cleared from the mouth by swallowing and/or

2. Nitroglycerin was removed in part by degradation or metabolism.

The relative amounts of drug removed by the two mechanisms could vary depending on the drug substance being delivered. Several other patents describing lingual sprays for analgesics¹⁰, caffeine¹¹, nicotine^{12,13}, nifedipine¹⁴, verapamil and gallopamil¹⁵, and a broad patent covering the use of 1,1,1,2,3,3,3-heptafluoropropane as a propellant¹⁶ have been issued but they were not accompanied by enough clinical data to allow judgments to be made as to which of the two pathways was operative. To our knowledge none of the products in those patents has been registered for marketing in any country.

If the first explanation was correct, then one would expect that other drugs which did not have the rapid penetrating properties of nitroglycerin and low molecular weight would not have enough time for absorption before they were cleared.

Therefore, lingual sprays containing these drugs could not deliver a therapeutically meaningful amount in the time before clearance from the oral cavity. If the second explanation was correct and the removal by degradation is a major pathway of clearance for nitroglycerin, then other drugs which were not as rapidly degraded might still have enough time prior to clearance for a therapeutically meaning amount to be absorbed. The I²R formulations were developed to explore which of these two possible explanations could be correct and for which products they may apply.

II. Immediate-Release (I²R) Formulations:

A. Manufacture : In the simplest terms these formulations are solutions of the drug substance in either a polar¹⁷ or non-polar¹⁸ solvent delivered by means of a pump aerosol spray or a propellant driven aerosol spray into the oral cavity. The manufacture of these formulations involves dissolving the drug substance plus other excipients such as flavors in a suitable solvent and placing this solution in a bottle or canister. A suitable metered dose valve is attached to the bottle or canister. If a propellant is used, it is added through the valve after the attachment of the valve. In-process controls involve assay to assure homogeneity of the solution prior to filling the bottle or canister. Particle size, dissolution testing and other such factors of concern for tablets and other solid dosage forms are not applicable.

B. Clinical results: A series of formulations have been prepared and tested in pharmacokinetic studies comparing them with the standard oral treatment or in pharmacodynamic studies comparing the therapeutic effects against the standard therapy. The following are the results of some of these studies.

- 1. Clemastine fumarate lingual spray.** A pharmacokinetic study was carried out comparing a clemastine fumarate oral tablet (2.68 mg) manufactured by Novartis Pharmaceuticals Corp. (Tavist®) with two activations of a lingual spray delivering 1.34 mg per. The mean 72-hour plasma levels show two peaks for the lingual spray and one for the tablet (Figure 1). The first peak in the mean plasma level curve after administration of the lingual spray is attributed to the absorption through the oral mucosa and the second, which is

similar to the mean plasma curve obtained after administration of the tablet, is attributed to absorption from the gastro-intestinal tract (GI tract). The clemastine that was not absorbed through the oral mucosa would be swallowed and absorbed from the GI tract. Figure 2 shows the first 90 minutes of the total 72-hour curve in Figure 1. The lingual spray delivers significant amounts of the drug within 5-10 minutes and the first peak is reached within 63 minutes (the lingual spray curve is off scale after 10 minutes) whereas the tablet only starts to deliver clemastine to the systemic circulation sometime between 20 and 30 minutes.

The mean Time-to-Maximum-Plasma Level (T_{MAX}) of the tablet was 7.0 hours. Just as the rate of mucosal absorption begins to decline, the absorption from the GI tract begins and builds on the plasma levels obtained by the mucosal absorption. Based on comparisons of the mean Area-Under-the Curve (AUC), the combined mucosal/GI absorption is 4.89 times larger than absorption after administration of the tablet. Since the duration of the therapeutic effect is dependent on the rate of elimination and not on the rate of absorption, both formulations should be effective over the same period of time. The half-life of elimination for the spray (15 hours), though slightly larger, is not significantly different from that of the tablet (11 hours). Table 2 summarizes the observed pharmacokinetic parameters.

- 2. Estradiol Lingual Spray.** A pharmacokinetic study was carried out comparing the plasma levels obtained after administration of an Estrace® tablet (2.0 mg) manufactured by Bristol-Meyers Squibb Co. and a lingual

spray delivering 2.0 mg of estradiol in a single activation. Figure 3 shows the relationship of the plasma levels obtained after administration of the tablet with the levels obtained after administration of the lingual spray. The spray achieved a mean C_{MAX} 75.8 (Table 2) times higher than the tablet with a mean T_{MAX} of 42 minutes whereas the mean T_{MAX} of the tablet was observed at 8.33 hours (Table 2). The mean AUC after the administration of the lingual spray was 9.6 times larger (Table 2) than the mean AUC after administration of the tablet. The plasma concentrations of estradiol and estrone obtained for the I²R formulation and the tablet respectively are shown in Figures 4 and 5. These figures show the effect of the first pass metabolism on the absorption of estradiol. The most abundant entity in the plasma after administration of the tablet (Figure 4) is the metabolite estrone (estradiol/estrone: 1.0:6.25) while the most abundant entity after administration of the I²R formulation is estradiol (Figure 5) (estradiol/estrone: 1.0:0.88). Figure 6 displays the relative amounts of estrone obtained after administration of the tablet and the spray. The amount of estrone in systemic circulation is about the same in terms of AUC (I²R/tablet: 1.28:1.0) as expected since the estradiol would be eventually metabolized to estrone, if not on the "first pass" through the liver, then on other passes or in the target tissues. Tables 3 and 4 summarize the pharmacokinetic parameters obtained for estradiol and estrone respectively.

3. Progesterone.

Once the results of the estradiol study were available the pharmacokinetic study comparing a 100 mg Prometrium® capsule with a I²R formulation containing progesterone had to be designed differently than the estradiol lingual spray study. If a 100 mg I²R formulation containing progesterone would deliver a mean C_{MAX} 70 times higher than the capsule, a distinct possibility existed that very high plasma levels would be reached which could lead to side effects. Therefore to produce blood levels approximately equivalent to the Prometrium® capsule, a I²R formulation delivering a lower dose was developed to compensate for the expected greater efficiency in progesterone lingual spray delivery.

The study employed the Prometrium® capsule delivering 100 mg of progesterone and I²R formulation delivering only 2.0 mg of progesterone. The results of this study are seen in Figure 7. The plasma levels after administration of the Prometrium® capsule, as measured by radioimmuno assay (RIA), were highly variable. A mean C_{MAX} was reached only at a mean T_{MAX} of 2.25 hours, while the mean T_{MAX} obtained after administration of the lingual spray was 32.3 minutes. The ratio of the AUCs after administration of the I²R formulation to that obtained after administration of the capsule was 0.43, indicating that on a per milligram dosed basis the lingual spray delivered 21.4 times more progesterone to the systemic circulation than the capsule and with much less variability. The pharmacokinetic parameters obtained are summarized in Table 5.

Discussion.

The results of the above studies demonstrate that nitroglycerin lingual sprays were not unique in their ability to deliver the drug substance through the oral mucosa efficiently in therapeutically meaningful amounts. In fact, with I²R formulations studied to date, the absorption rate starts to decrease in about 30-60 minutes. This decrease could be due to a decrease in the fraction of the drug available for absorption because of absorption, or due to clearing of the mouth by swallowing or both. In the case of clemastine the clearing of the mouth is certainly playing a role as seen in the large wave of clemastine arriving in the plasma at the later time periods by absorption from the GI tract. In the case of estradiol and progesterone it is more difficult to see this GI absorption because of the larger first pass effect experienced by these two drugs. The more lipophilic the drug substance the larger is the amount that will be absorbed through the mucosal membrane relative to the standard immediate release formulation. Clemastine fumarate is an amine salt with some solubility in water and soluble in alcohol whereas estradiol and progesterone are completely insoluble in water.

The most plausible series of events to explain the absorption process and the apparent limit of about 30-60 minutes for the absorption phase is the following:

1. The lingual spray delivers a mist of fine droplets onto the mucosal membrane, probably onto the mucin layer.
2. The solvent either is absorbed through the membrane possibly taking some of the drug substance with it or it is diluted by the saliva or both.

3. The drug substance that was in the solvent and was not immediately absorbed is deposited as a thin film onto the mucin layer covering the membrane² which probably acts as a natural muco-adhesive and binds the drug to the membrane.
4. The drug substance can then diffuse into the lipid layer in the membrane⁶ and from there into the systemic circulation.
5. Alternately, the drug can dissolve in the saliva and be transported into the stomach on swallowing or as the mucin layer is sloughed off and replaced by new material, the drug can be transported with the sloughed layer into the stomach.

The principle that equal plasma levels give equal therapeutic results is the basis of all generic drug approvals for solid oral dosage forms that give a blood level. When plasma level curves parallel each other, one can also conclude that the time profile of the therapeutic effect will also be the same. If the profiles are different, then the timing of the therapeutic effect will also be different. Based on these principles and the results of the above studies, one would predict that the amount dosed could be reduced by as much as 3 fold in the case of clemastine, 10 fold in the case of estradiol and 20 fold in the case of progesterone and expect the same efficacy. One might also expect that the lingual sprays would have a faster onset of therapeutic effect as a result of the very fast raise in plasma levels. These possibilities are presently being investigated.

Summary:

Like sustained-release formulations, I²R oral dosage forms will allow new indications and breathe new life into existing therapies. For example, conventional oral drugs often are used in maintenance dosing regimens because the time to onset of a therapeutic effect is long. With this lag in therapeutic effect the patient would often rather use a maintenance program with the concurrent exposure to unnecessary amounts of drug substance than risk suffering symptoms for hours while waiting for relief.

I²R formulations may allow rapid, dosing-as-needed treatments (PRN dosing) because fast onset would be the rule rather than the exception. I²R formulations will avoid the first pass effect bypassing the liver for that fraction of the drug absorbed trans-mucosally and allow one to use much smaller doses and achieve the same therapeutic effect. As noted above the lower dose is most important where metabolism leads to reactive intermediates which can bind irreversibly to DNA and/or RNA or other body components. The I²R formulations also lend themselves to the development of more convenient drug therapies for geriatric and pediatric patients as well as treatments for patients who are not able to take solid medications by mouth.

Some examples of candidate compounds suited for lingual spray application on the basis of the need for fast treatment or relief of symptoms and/or the ability to

deliver the same therapeutic effect with a lower dose are antihistamines, steroid hormones, antidepressants, sedatives, and the like (see Table 6).

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17. H. Dugger. Buccal Polar Spray or Capsule. Patent US 6,110,486. Issued August 29, 2000.

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Table 1 - Unique advantages - Oral Lingual Spray

Characteristic	Lingual Spray	Nasal Spray	Fast-Dissolve Tablets	Buccal Patches	Inhalers
Rapid blood levels	YES	Maybe	No	Maybe	Maybe
High bioavailability	YES	No	No	Probably	No
Avoids first pass	YES	No	No	Yes	Maybe
Lower dosing	YES	No	No	Maybe	No
Long term stability	YES	Maybe	No	Yes	Maybe

Table 2: Clemastine Pharmacokinetic Parameters after Administration of a Clemastine Fumarate Lingual Spray (2x1.34 mg) and a Tavist® Tablet (2.68 mg)
[N = 8]

	AUC(0-72hrs) (ng/mL/hr ⁻¹)			T _{max} (last peak)* (hr)			C _{max} (last peak)* (ng/mL)		
	SPRAY LS	TABLET	RATIO LS/T	SPRAY LS	TABLET	RATIO LS/T	SPRAY LS	TABLET	RATIO LS/T
Mean	20.99	7.57	4.89**	7.00	7.0	1.05	0.81	0.350	3.64
Standard Error	1.88	1.74	2.36	0.68	0.72	0.056	0.128	0.078	1.58
Median	19.49	6.89	2.44	8.00	8.0	1	0.83	0.332	2.02
Standard Deviation	4.61	4.62	5.78	1.67	1.91	0.136	0.313	0.206	3.88

*In the plasma curve of the Lingual Spray an additional peak was observed at a mean T_{MAX} of 1.0 hours with a mean C_{max} of 0.64 ng/mL

**Mean of the ratios.

Table 3: Estradiol Pharmacokinetic Parameters After Administration of an Estradiol Lingual Spray (2.0 mg) and an Estrace® tablet (2.0 mg).

[N = 6]

	AUC(0-24hrs) (pg/mL/hr ⁻¹)			T _{max} (hr)			C _{max} (pg/mL)		
	SPRAY LS	TABLET	RATIO LS/T	SPRAY LS	TABLET	RATIO LS/T	SPRAY LS	TABLET	RATIO LS/T
Mean	7769	856	9.6	0.71	8.33	0.10	3322	47.4	75.8
Standard Error	1493	141	0.8	0.08	1.28	0.01	524	8.7	7.7
Median	7827	826	9.0	0.75	8.00	0.10	3215	45.5	76.5
Standard Deviation	3658	344	1.9	0.19	3.14	0.02	1285	21.3	17.3

Table 4: Estrone Pharmacokinetic Parameters After Administration of an Estradiol Lingual Spray (2.0 mg) and an Estrace® tablet (2.0 mg).

[N = 6]

	AUC(0-24hrs) (pg/mL/hr ⁻¹)			T _{max} (hr)			C _{max} (pg/mL)		
	SPRAY LS	TABLET	RATIO LS/T	SPRAY LS	Tablet	RATIO LS/T	SPRAY LS	TABLET	RATIO LS/T
Mean	6777	5275	1.28	2.25	6.17	0.45	505.00	368.50	1.53
Standard Error	620	600	0.10	0.66	1.17	0.17	59.55	58.17	0.23
Median	6898	5352	1.33	2.00	5.00	0.40	488.00	354.50	1.63
Standard Deviation	1518	1469	.022	1.60	2.86	0.37	145.87	142.50	0.51

**Tabl 5: Progesterone Pharmacokinetic Parameters After Administration of an
Progesterone Lingual Spray (2.0 mg) and a Premetrium® Capsule (100.0 mg).**
[N = 4]

	AUC(0-24hrs) (ng/mL/hr ⁻¹)			Tmax (minutes)			Cmax (ng/mL)		
	SPRAY LS	Capsule	RATIO LS/T	SPRAY LS	Capsule	RATIO LS/T	SPRAY LS	Capsule	RATIO LS/T
Mean	1005.8	2408.3	0.43	32.5	135.0	0.40	7.87	13.6	0.62
Standard Error	134.8	226.1	0.06	4.3	56.8	0.15	1.25	2.9	0.12
Median	1077.5	2262.5	0.46	30.0	90.0	0.38	7.99	11.8	0.59
Standard Deviation	269.6	452.2	0.12	8.7	113.6	0.29	2.49	5.9	0.24

Table 6 – Some Examples of Drugs Where Fast Onset and/or Lower Dose Would be Important

Antihistamines:

clemastine
chlorpheniramine,
dexchlorpheniramine
loratadine

Antidepressants:

fluoxetine (Prozac)
buspirone (Buspar)

Biologically Active Amines:

bromocriptine
apomorphine
selegiline
amitriptyline
dopamine precursors
serotonin precursors

Peptides:

cyclosporine
insulin
calcitonin

Anorexiant:

dextroamphetamine
phentermine
mazindol
sibutramine

Sleep Inducers:

temazepam
doxylamine
zolpidem
triazolam
nitrazepam

Cardiovascular Agents:

nitrates (nitroglycerin)
ACE inhibitors
calcium antagonists
beta blockers

Sedatives:

barbiturates
benzodiazepines

Steroids:

testosterone
estradiol
progesterone
combinations of the above

Antinauseants:

prochlorperazine
chlorpromazine
perphenazine

Decongestants:

dextromethorphan
pseudoephedrine

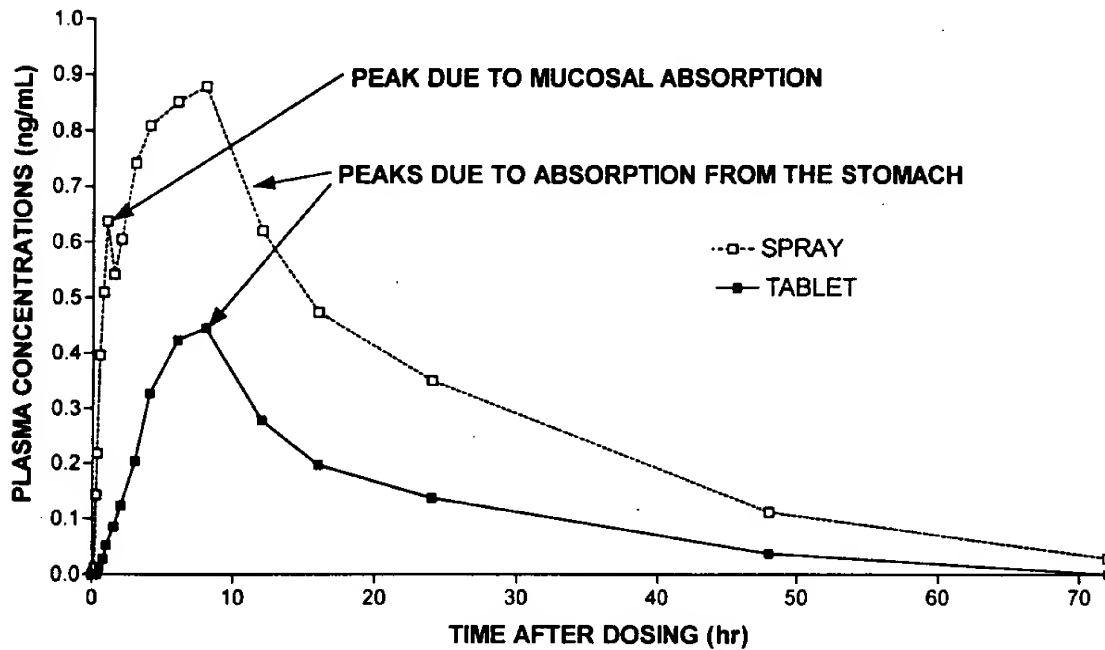
Nutritionals:

vitamins
calcium supplements
iron supplements

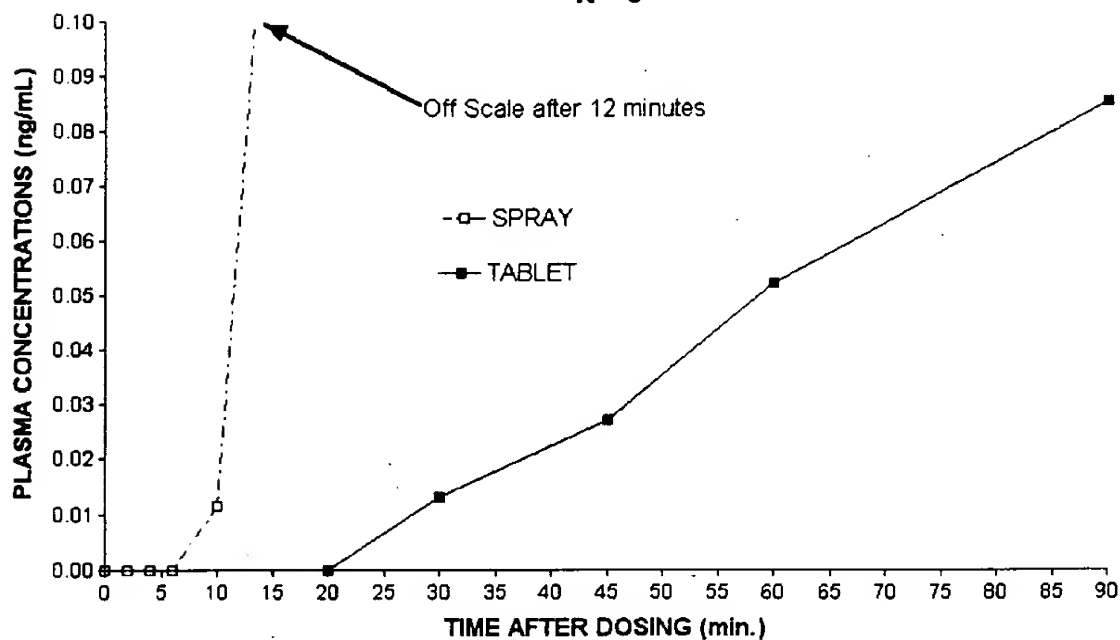
Immediate-Release (I²R) Lingual or Buccal Spray Formulations
for Transmucosal Delivery of Drug Substances

Figures:

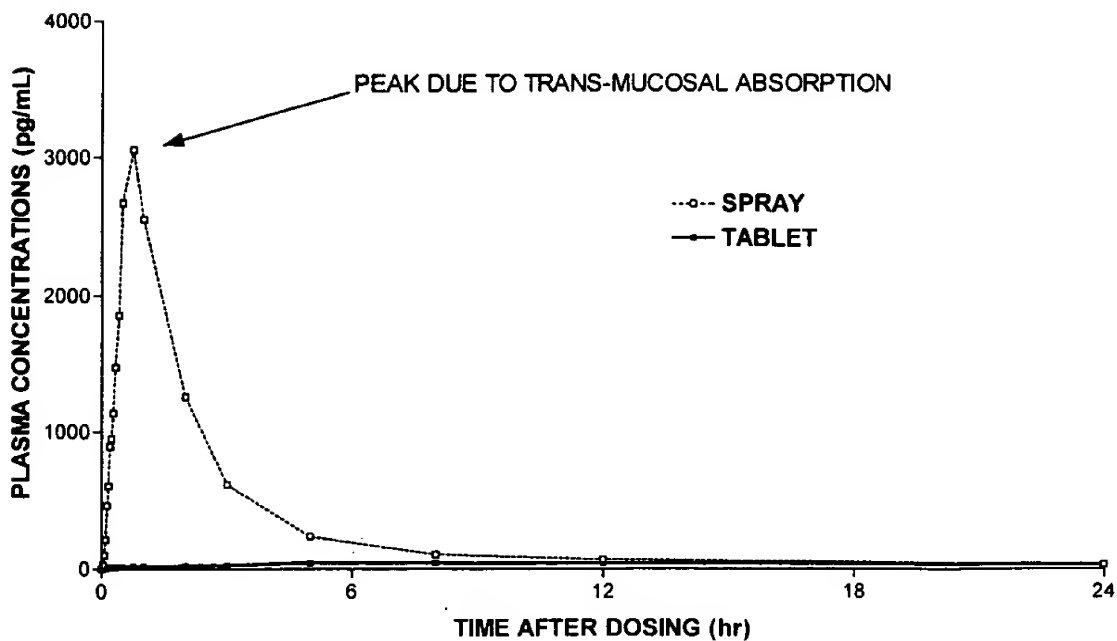
Figure 1: Mean Plasma Levels of Clemastine after Administration of a Clemastine Lingual Spray (2x1.34 mg) and a Tavist^(R) tablet (2.68 mg)
N = 8



**Figure 2: Mean Plasma Levels of Clemastine after Administration of a Clemastine Lingual Spray (2x1.34 mg) and a Tavist^(R) tablet (2.68 mg)
N = 8**



**Figure 3: Mean Plasma Levels of 17-beta-Estradiol after Administration of a Lingual Spray (2.0 mg) and an Estrace^(R) Tablet (2.0 mg)
N = 6**



**Figure 4: Mean Plasma Levels of 17- β -Estradiol and Estrone after Administration of an Estrace (R) Tablet (2.0 mg)
N = 6**

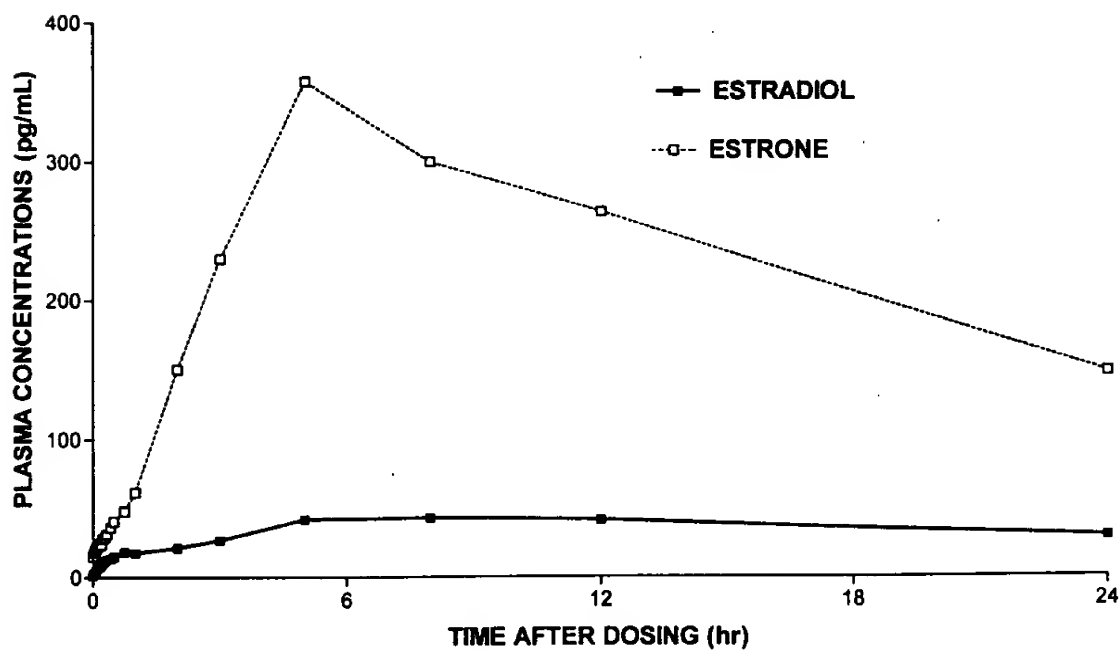


Figure 5: Mean Plasma Levels of 17-beta-Estradiol and Estrone after Administration of a Lingual Spray (2.0 mg)
N = 6

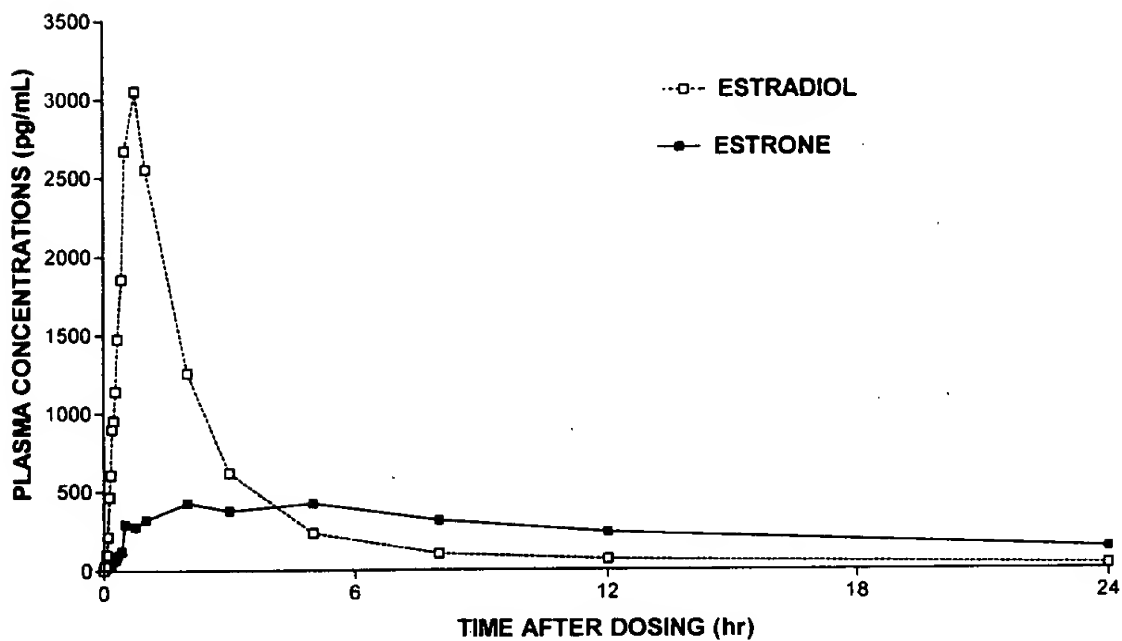


Figure 6: Mean Plasma Levels of Estrone after Administration of a Lingual Spray (2.0 mg) and an Estrac (R) Tablet (2.0 mg)
N = 6

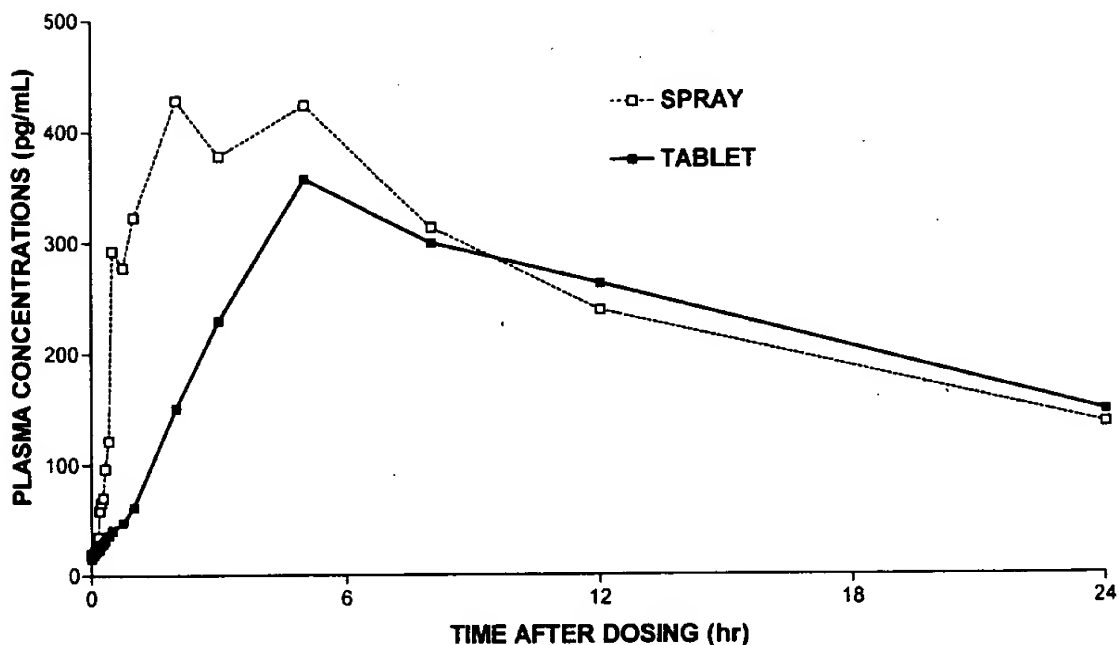


Figure 7: Mean Plasma Levels of Progesterone after Administration of a Progesterone Lingual Spray (2.0 mg) and a Prometrium^(R) Capsule (100 mg)
N = 4

